

4 /

--The immune system contains a system of DCs that is specialized to present antigens and initiate several T cell-dependent immune responses. DCs are distributed widely throughout the body in various tissues. DCs are found in nonlymphoid organs either close to body surfaces, such as in the skin and airways, or in interstitial regions of organs like heart and liver and can migrate via the blood and lymph to lymphoid organs (*see* Austyn et al., 1988, *J. Exp. Med.* 167:646, Larsen et al., 1990, *J. Exp. Med.* 171:307 and Austyn and Larsen, 1990, *Transpl.* 49:1-7). There, antigens can be presented to T cells in the recirculating pool which, in turn, leads to an immune response (*see* Inaba et al., 1990, *J. Exp. Med.* 172:631).—

Please replace in paragraph 8 on page 4, with the following rewritten paragraph:

A<sub>2</sub>

--While DCs classically promote immune responses, they can be manipulated to induce antigen-specific hyporesponsiveness *in vitro*. The ability to manipulate the state of DC maturation *in vitro* has led to attempts to induce tolerance by administration of costimulatory molecule-deficient DCs in animal models of pancreatic islet cells or organ transplantation. *See* Fu et al., *Transplantation* 62:659-665 (1996); Rastellini et al., *Transplantation* 60:1366-1370 (1995); Lu et al., *Transplantation* 64:1808-1815 (1997); Gao et al., *Immunology* 98:159-170 (1999); Hirano et al., *Transplant Proc.* 32:260-264 (2000); Thomson and Lu, *Transplantation* 68:1-8 (1999). While these methods have had modest success, tolerance has not been achieved. This

A, may be due to the late maturation/activation of DCs with upregulation of costimulatory molecules upon encountering a host microenvironment rich in pro-inflammatory mediators. The ability to manipulate the state of DC maturation may also be useful for the treatment of other diseases involving inflammatory events, such as autoimmune arthritis, asthma, septic shock, lung fibrosis, glomerulonephritis, atherosclerosis and AIDS.--

---

Please replace in paragraph 20 on page 9, with the following rewritten paragraph:

---

A, --Langerhans cells (LCs) are specialized epidermal cells with dendritic morphology. GM-CSF and interleukin 1 mediate the maturation of murine epidermal LCs into potent immunostimulatory dendritic cells. Heufler et al., 1987, *J. Exp. Med.* 167:700-705). In addition, LCs in the epidermis which are specialized for antigen uptake and processing, are immature. Upon exposure to reactive haptens, LCs in the epidermis rapidly migrate to draining lymph nodes (DLNs) where they begin to exhibit mature features to develop into DCs. See Banchereau & Steinman, 1998, *Nature* 392:245-252. Chemokines and chemokine receptors are thought to control DC migration, which is essential for their maturation. See Ngo, 1999, *J. Exp. Med.* 189:403-412. Despite the above technologies, ex vivo Dc strategies have significant inadequacies that are overcome by the present invention.--

---

## PATENT

Please replace in paragraph 46 on page 19, with the following rewritten paragraph:

AW --As used herein, an APC stimulating factor is capable of stimulating APC migration and/or maturation. Nonlimiting examples of APC stimulating factors include reactive haptens; cytokines such as tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and Interleukin 1 (IL-1); bacterial products such as lipopolysaccharide (LPS) and lipoproteins (LPs) and ultraviolet radiation. See Smedt et al., 1996, *J. Exp. Med.* 184:1413-1424; Shornick et al., 1996, *J. Exp. Med.* 183:1427-1436; Cumberbatch & Kimber, 1994, *Immunology* 81:395-401; Cumberbatch & Kimber, 1992, *Immunology* 75:257-263; Stoitzner et al., 1999, *Journal of Leukocyte Biology* 66:462-470. As used herein, a reactive hapten is a molecule capable of stimulating APC migration and as acting as an antigen. Nonlimiting examples of reactive haptens include dinitrofluorobenzene (DNFB), fluorescein isothiocyanate (FITC), FITC, oxazolone and urushiol. In one embodiment of the present invention, the reactive hapten may be DNFB or FITC.--